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Report two case of lymphangioleiomyomatosis (LAM) with presentation of recurrent pneumothorax

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Abstract

Pulmonary Lymphangioleiomyomatosis (LAM) is a rare and female-dominant disease and associated with smooth muscle cell proliferation, (LAM) which presents with diffuse progressive destruction of the pulmonary parenchyma. The incidence is less than 1 per million, which results in cystic lung disease and presente commonly with dyspnea and pneumothorax. Work up for diagnosis and exclusion other disease as: Sjögren's syndrome type A, B and mazement of angiotensin-converting enzyme (ACE) levels, alpha-1-antitrypsin levels, and vascular endothelial growth factor (VEGF) anti bodies. Definitive diagnosis limited only to tissue sampling. No effective treatments are currently proposed for this disease. Two 49 and 39year-old woman who was referred with recurrent pneumothorax, after thoracotomy and resection, diagnosed was made with pulmonary Lymphangioleiomyomatosis. After pulmonary Lymphangioleiomyomatosis was performed, they treated with anti-estrogen therapy and symptomatic supportive care. In follow up pneumothorax was not occurred again. Pulmonary Lymphangioleiomyomatosis is a very rare disease that cannot be effectively cured.

Keywords: Pulmonary Lymphangioleiomyomatosis; Pathological examination; Immunohistochemistry; Anti estrogen therapy

1 Introduction

Lymphangioleiomyomatosis (LAM) is a disorder involve multiple organ systems, such as the kidney and lymphatics system of lung [1-2]. Pulmonary Lymphangioleiomyomatosis (LAM) is a rare hamartoma Tous proliferation of the smooth muscle involved in blood vessels and lymphatics in the lung (1,2).Patients who have LAM without tuberous sclerosis, they have abnormal proliferation of smooth muscle cells [2]. It extends into the pulmonary interstitium, leading to diffuse thin-walled cystic lesions and pulmonary hemorrhage, and lymph node involvement may can result in chylous effusion (3). LAM affected women in reproductive age [2-.3) After lung ,LAM mostly involved kidneys, may present as abdominal tumors which called angiomyolipomas [2, 3,11].LAM is clinically characterized by progressive dyspnea, cough, chest pain, hemoptysis and pneumothorax, leading to progressive airflow obstruction and impaired lung diffusion function, culminating in respiratory failure commonly in premenopausal women (4,5). Chest radiographs show diffuse interstitial infiltrates and thin-walled cystic lesions. Pulmonary function tests usually reveal obstructive ventilation dysfunction and airflow limitation with impaired lung diffusion function2-.3) . LAM is considered to occur alone or is associated with tuberous sclerosis (6). The pathogenesis of LAM has not been clearly clarified and its treatment remains limited [9]. The most common extrapulmonary manifestation was retroperitoneal lymph node

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involvement (52.1%); the most common chest imaginges finding are multiple different sized thin-walled cystic shadows in whole lungs (93.8%); the most common lung biopsy method was bronchoscopic biopsy (41.0%); However, pulmonary function tests, radiographic findings, clinical presentation, and pathological studies have aided in its diagnosis (3,10,11). But definitive diagnosis is with open lung biopsy (8). In the patients with pulmonary dysfunction, obstructive ventilation dysfunction was 65.1%, and diffusion dysfunction was 38.4% (4,5). However, there is no effective medical therapy, and lung transplant may be the only possible treatment for the cure of patients with LAM (7,8).Management consists of supportive care, such as stop smoking , vaccination against influenza and pneumococcal, stop heavy exercise, physiotherapy and rehabilitation of lung, avoiding airplane travel, maintaining healthy ,weight and diet and support psychosocial conditions of LAM patients[4-5]. Patients may receive anti-estrogen therapy to suppress respiratory system progression and pleurodesis to prevent complications such as pneumothorax [3-4]. Traditionally, LAM was managed via lung transplantation exclusively; LAM is a disease that can be difficult to manage and can have a poor prognosis [9].

2 Case one

A 36-year-old female in north of Iran present with exertion dyspnea, which occurred from four month prior and progressed and dyspnea was increased. She had two child birth without and difficulty. The patient did not have fever, chills, cough, chest pain and hemoptysis. Due to worsening of symptoms, the patient referred Department of Respiratory for visited of pulmonologist (in private hospital of Arya north of Iran). The patient had a history of pneumothorax and tube thoracotomy 11 month ago and had no history of smoking, addiction, alcohol consumption any drug. Physical examination show decreased breast sound on the right side and others organs was normal. The laboratory findings including routine tests of blood, liver and kidney function tests were normal. analysis of arterial blood gas showed slight hypoxemia, the oxygen saturation of patient was 90% on room air**.** (Pulmonary function tests showed milled obstructive lung disease. Firstly, Chest CT show bilateral, diffuse and thin-walled cystic changes and right side pneumothorax (Fig. 1A, B,C).fibro- optic bronchoscopy was performed and no abnormality was found in the bronchial lumen. The patient was not diagnosed by the fibro- optic bronchoscopy biopsy, because the size of the specimen was small. Based on the chest CT -scan, right poster lateral thoracotomy performed for recurrent pneumothorax treatment, lung biopsy was need for definitive diagnosis, treatment of pneumothorax resection of cystic lesions if possible, pleurectomy and pleurodesis for prevention of pneumothorax (FigE,F) . Due to the CT findings, the pathology examination of the biopsy specimen show hyperplasia of smooth muscle , proliferation of spindle cells around small blood vessels, lymphatic vessels and respiratory bronchioles (Fig 3 A). Immunohistochemistry (IHC) demonstrated that characteristic smooth muscle cells were positive for smooth muscle actin (SMA), human melanoma black (HMB) 45 and D2-40. These findings show the diagnosis of LAM. Patient underwent to anti estrogen by pulmonologist, which improved the dyspnea and pulmonary function show better. However, the patient with LAM in any stage of the disease requires long-term follow-up, because there is not any effective and curative surgical and medical therapy for LAM. The left side for possibility of occurrence of pneumothorax, pleudesis was performed by Betadin20%. During two years follow –up the condition of patient was good (Fig4). This case report was approved by the local ethics review committees of Arya hospital, and patient let us to report this case.

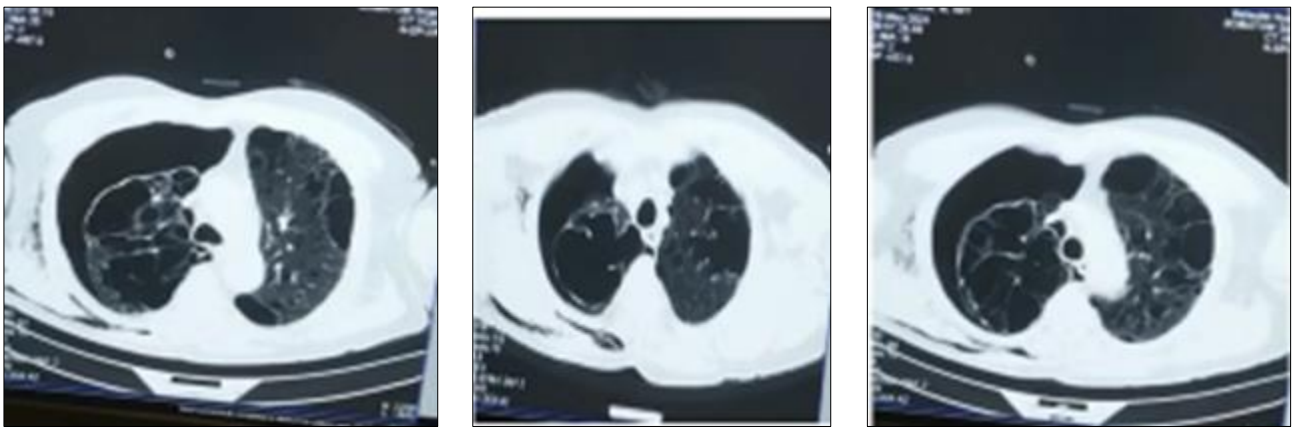

Figure 1 Case one: A, B, C. show CT-scan CT show bilateral, diffuse and thin-walled cystic changes and right-side pneumothorax

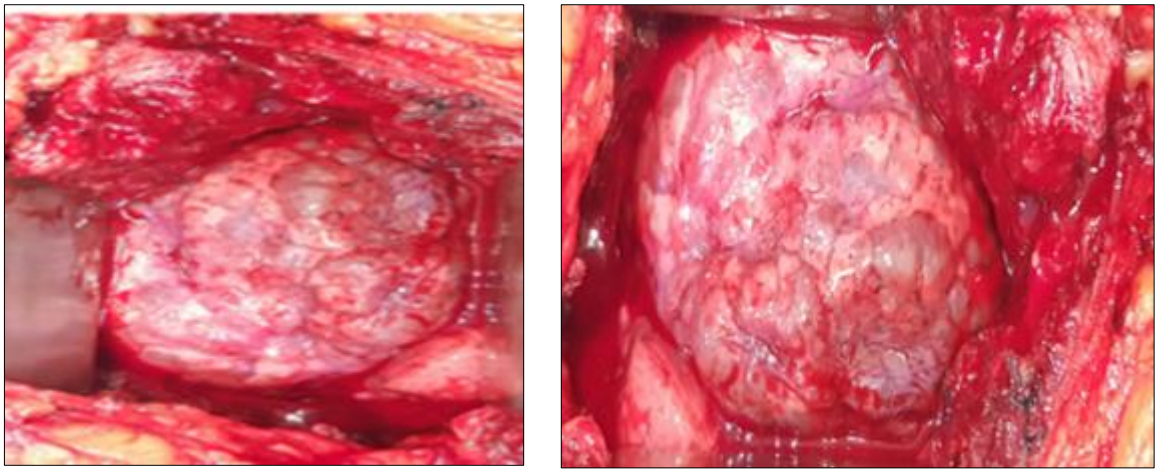

Figure 2 Case one: show intraoperative of lung with multiple variation of cystic lesion

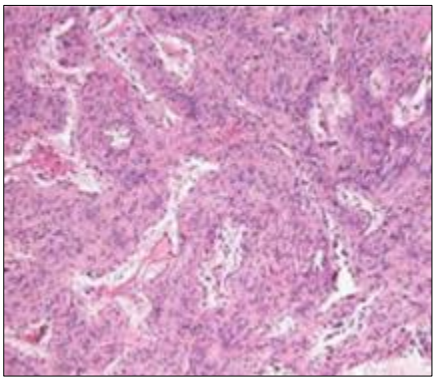

Figure 3 Case one: CT findings, the pathology

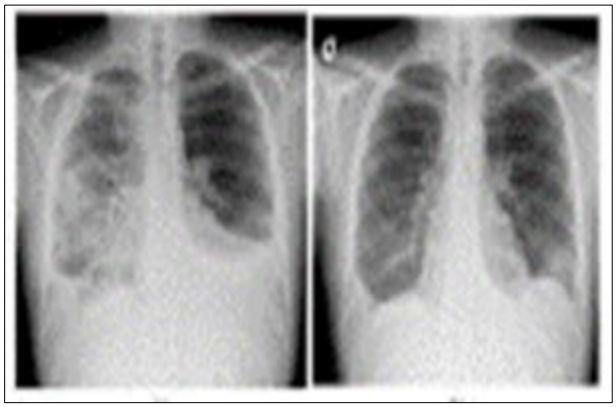

Figure 4 Case one: CXR show two-month post-surgery pathology

Figure 4 The pathology examination of the biopsy specimen shows hyperplasia of smooth muscle, proliferation of spindle cells around small blood vessels, lymphatic vessels and respiratory bronchioles**.**

3 Case two

A 32-year-old female presented to the emergency department with a chief complaint of two days of sharp, right-sided chest pain which radiating to her right neck and right upper back associated with shortness of breath and an episode of faint attack. Past medical history was significant for chronic sinusitis which was treated two months prior to her presentation and right-side pneumothorax one years ago which treated by tube thorcostomy. Family history was insignificant. The patient was never used smoke, opium and alcohol. She lived a very healthy, active lifestyle. In the emergency department the patient has respiratory distress, the oxygen saturation of patient was 91% on room air. The physical exam was significantly diminished lung sounds, especially in right pulmonary fields. Chest X-ray (Figure (Figure1) and computed tomography (CT) of chest(Fig1 A,B) show multiple cystic air space lesion in both lung and large right pneumothorax which requiring urgent tube thoracotomy. She was referred to pulmonology department with a right-sided chest tube and on nasal oxygenation for others management and evaluation of her recurrent of pneumothorax and severe air space lesion in both lungs. Pulmonologist and thoracic surgery were consulted for examination of this case. Abdominal Workup with ultrasound was negative for renal angiomyolipoma, screen for human immunodeficiency virus (HIV) was negative, alpha-1-antitrypsin and angiotensin-converting enzyme (ACE) levels was normal and anti-Sjögren's syndrome type A, type B was normal. Diagnosis was suspected to Lymphangioleiomyomatosis (LAM). For treatment of pneumothorax and definitive diagnosis, Patient underwent surgery with right posterolateral thoracotomy wedge excision of lower lobe and others airspace lesion was resected, pleurectomy and abrasion procedure was performed to prevent air leaks and recurrences of pneumothorax postoperatively (Fig2 C, D). Left side of lung underwent pleuredesis by provide idon for prevention of pneumothorax, all spaceman was sent to pathology department. Patient was extubated successfully in operation room and with nasal oxygen referred to intensive care unit. Postoperative course was uncomplicated. Pathologic, examination of the specimen was lung parenchyma with cystic changes and cystic structures. These structures were covered by a group of epithelioid to spindle eosinophilic cells (Fig 3 E). Immunostaining showed these cells were positive for actin and progesterone receptors and with human melanoma black. With All of these pathologically features the diagnosis were Lymphangioleiomyomatosis. The patient was successfully discharged home on nasal cannula oxygen with follow –up evaluations. Postoperative recommendation included: limiting air travel. Antisterogen therapy was stated by pulmonologist. Follow-up chest X-rays 2 ,4 ,8 months following hospital discharge showed negative for pneumothorax (Fig4 F, G) This case report was approved by the local ethics review committees of Arya hospital, and patient let us to report this case.

Pathologic, examination of the specimen was lung parenchyma with cystic changes and cystic structures. These structures were covered by a group of epithelioid to spindle eosinophilic cells Fig4 H, Pulmonary histopathological findings of LAM: The right side of the panel demonstrates HMB45 Histopathology of the lung showing cystic lesions and smooth muscle cell-like infiltrates on the walls of the cysts and showing the characteristic spindle and epithelioid LAM cells. A and B: Pathological features showing abnormal smooth muscle cells lining the airways, lymphatics, and blood vessels, leading to airflow obstruction.

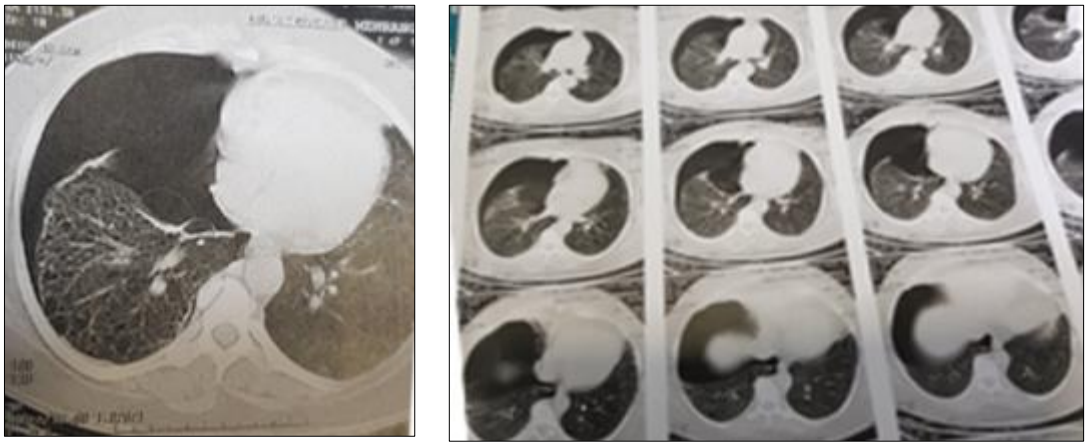

Figure 5 Case two: A, B show CT of chest multiple cystic lesion and pneumothorax

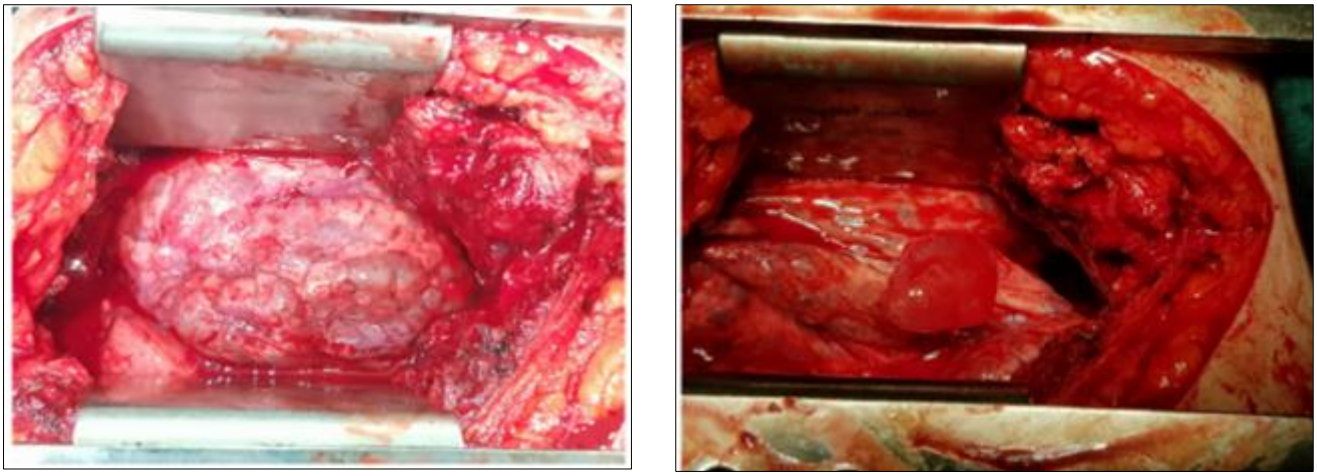

Figure 6 Case two: C, D show multiple cystic lesions in vaeirtion size in intraoperative

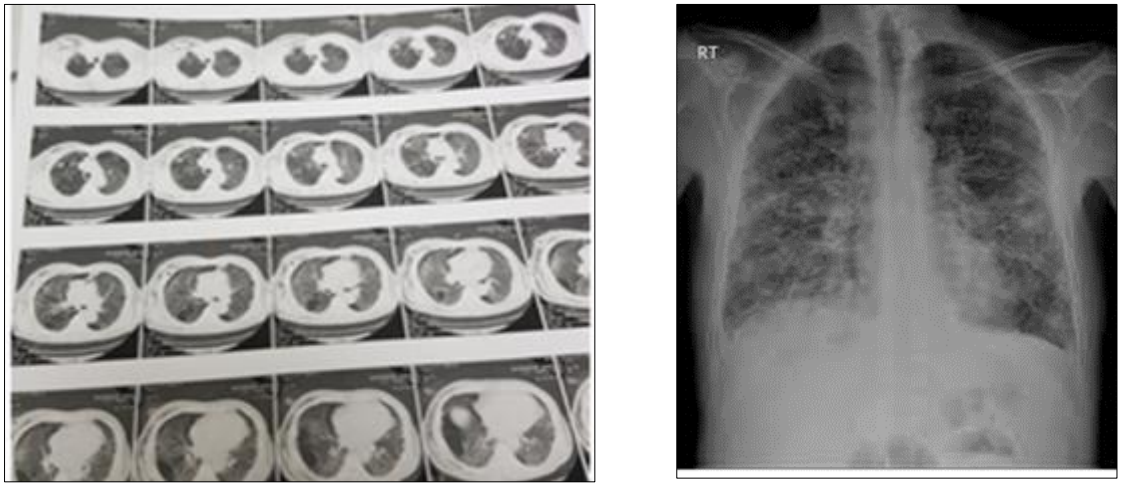

Figure 7 Case two: E, F show CT-can and CXR after one month and four months postoperative

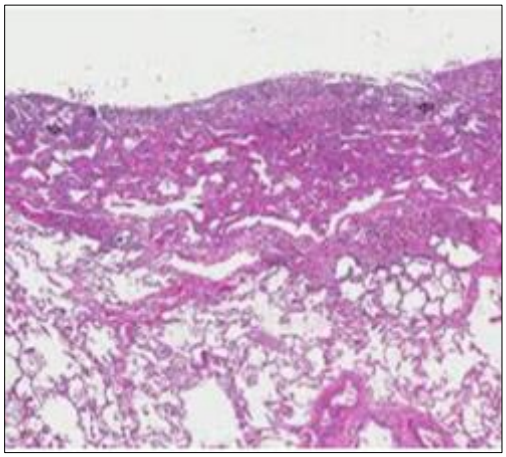

Figure 8 Case two: H: Pathological features showing abnormal smooth muscle cells lining the airways, lymphatics, and blood vessels, leading to airflow obstruction

4 Discussion

LAM is a rare disease may affect lung and others organs especially in female gender. LAM might have not specific clinical presentation in early stage. Our two patients were female which were in childbearing ages which present with pulmonary manifestations. LAM is estimated to have an incidence of one case per 1,000,000 patients in some country as USA and Europe (17,18). Diagnosed of LAM is potentially changing (3,10,11,17). After lung ,LAM mostly involved kidneys and present as abdominal tumors which called angiomyolipomas [2, 3,11]. LAM may be mistaken in early exercise testing stage with other pulmonary disorders , because initial presenting symptoms in LAM is similar in others disorder as obstructive or restrictive diseases of pulmonary, and it not response to bronchodilators therapy [1-2]. LAM patients who undergo excesses , may become hypoxemia with difficulty in ventilation and gas exchange [3]. Pulmonary function testing show decrease in forced expiratory volume in 1 second (FEV1) and (DLCO) [4]. Radiographic imaging as CXR and CT –scan of chest show hyperinflated lungs and multiple thin-walled cysts air filed lesion in pulmonary parenchyma [(3,4,10,11).When approaching for presentation dyspnia and diagnosis of lung involvement , others organs should be evaluated as angiomyolipoma kidney[2, 3,11] . Patients who present with LAM in older age and have a presence of angiomyolipoma in kidney to have a lower mortality risk [11). Congenital LAM presents as a more aggressive disease commonly affecting the brain, kidney, and integumentary systems, common pulmonary manifestations are low [8,9) .LAM cells morphologically consist of either myofibroblast spindle cells or epithelioid polygonal cells, which can proliferate and lead to alveolar air restriction(3,7,10,11,17). Pulmonary lymphangioleiomyomatosis occurs almost exclusively in women of childbearing age, indicating that it is closely associated with estrogen(3,8,9,17). Pregnancy is thought to aggravate the condition [3,8], and it can improve after menopause [9]. Estrogen directly activates early phase ERK through non-genetic pathways [10,17].

During recent decade diagnosis and treatment of LAM has undergone some changes(9,11) . In the last decade the classification of LAM was as an interstitial lung disease but now LAM is a low progressive neoplastic disease that can metastasize [4,10, 11,18). Diagnosis tools for LAM include (3,10,11) : CXR, High- resolution CT (HRCT) scan is which the most accurate available imaging test for diagnosing (more than 80% of the time). Abdominal CT scan or ultrasound is recommended to evaluate for detect kidney mass (angiomyolipomas),(which are found in about 40 %),in our patient kidney was normal ,VEGF-D blood-based test can distinguish LAM from other cystic lung diseases that present with similar HRCT scan appearances this test not available in our hospital, An alpha-1 antitrypsin level ,this test in our patients was normal , Lung biopsy involves removing samples of lung tissue to examine for abnormalities that may indicate LAM with Thoracoscopy , Transbronchial biopsy and Open biopsy with thoracotomy(3,10,11,17). The diagnostic features were nodular proliferation of smooth muscle cells, dilated pulmonary lymphatic vessels, and the formation of air cysts. The smooth muscle nodules were in the wall of the affected lymphatic vessels and cellularity is higher in these nodules than in the bronchial smooth muscle (3,9,17).In our patients we performed thoracotomy ,wedge resection ,pleurectomy , pleural abrasion , conteral chest-tube insertion and pleurodesis for prevention of pneumothorax.

Report of pathologist was LAM. The recommendation is that patients with LAM need contralateral pleurodesis after their initial pneumothorax rather than waiting for a course pneumothorax before intervening with a pleural symphysis procedure(11) . Patients with LAM who experience spontaneous pneumothorax have a higher risk of recurrence and, therefore, pleurodesis is an available option to prevent further pneumothorax and complications through lung re-expansion after chest-tube insertion [12,13,14) .If patients do not respond to these medical therapy and health care , should referred for lung transplantation, our patients response partially to medical therapy and health care, A medication called Afinitor (everolimus) is a form of sirolimus that may help reduce the symptoms of tuberous sclerosis LAM. It is not approved by the Food and Drug Administration (FDA) for this purpose, but healthcare providers can use it (10,14,16) .Imatinib is a type of cancer wroth blocker called tyrosine kinase inhibitor (TkI) can used.(10,14,16) . As LAM progresses, some females will need supplemental oxygen or asthma medications as bronchodilators (5,15). In patients whose lung function is severely poor, a lung transplant can extend life expectancy(5,14,17) .Our patients referred to pulmonologist for follow-up. Pulmonologist prescribe anti estrogen (Tamoxofen 20 MG daily With therapeutic serum levels of sirolimus and medication compliance, this immune modulator can prevent further pneumothorax incidents [14,15,16]. Imatinib is a type of cancer growth blocker called a tyrosine kinase inhibitor (TKI) is another medication used in LAM patients(19).Pneumothorax not occurred and general condition was better,

5 Conclusion

Lymphangiomyomatosis is a rare disease in young women that can present with spontaneous pneumothorax and dyspnea on exertion. The definitive treatment for this disease requires a lung transplant. If patients forgo transplant or are not transplant candidates, they can be managed pharmacologically with sirolimus, imatinib and tamoxofen.

Recurrent pneumothoraces can be prevented with pleurodesis and avoidance of air travel. The goal of this case report is to improve the diagnosis of this condition by considering LAM as a differential diagnosis for reproductive-age female patients that present similarly to our patient presented in this case report. Subsequently, this should lead to further research and increased treatment options for LAM patients.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

This case Report Approved by Teaching and Ethic comity of ARYA Hospital.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

References

[1] Yamazaki A, Miyamoto H, Futagawa T, An early case of pulmonary lymphangioleiomyomatosis diagnosed by video-assisted thoracoscopic surgery.. Ann Thorac Cardiovasc Surg. 2005; 11:405–407.

[2] Hohman DW, Noghrehkar D, Ratnayake S. . Lymphangioleiomyomatosis: a review.. Eur J Intern Med. 2008; 19:319–324.

[3] Taveira-DaSilva AM, Moss Epidemiology, pathogenesis and diagnosis of lymphangioleiomyomatosis. J. Expert Opin Orphan Drugs. 2016; 4:369–378. [

[4] Taveira-DaSilva AM, Steagall WK, Moss J , Lymphangioleiomyomatosis. Cancer Control. 2006; 13:276–285.

[5] McCormack FX, Gupta N Sporadic lymphangioleiomyomatosis: treatment and prognosis. . 2020;[Epub]

[6] Moss J, Avila NA, Barnes PM, et al. Prevalence and clinical characteristics of lymphangioleiomyomatosis (LAM) in patients with tuberous sclerosis complex. Am J Respir Crit Care Med. 2001; 164:669–671.

[7] Tanaka H, Imada A, Morikawa T, Shibusa T, Satoh M, Sekine K, Abe S. Diagnosis of pulmonary lymphangioleiomyomatosis by HMB45 in surgically treated spontaneous pneumothorax. . Eur Respir J. 1995; 8:1879–1882.

[8] Satria MN, Pacheco-Rodriguez G, Moss J. Pulmonary lymphangiomatosis. Lymphat Res Biol. 2011;9(4):191-3. doi: 10.1089/lrb.2011.0023. PMID: 22196284; PMCID: PMC3246407

[9] Martignoni G, Pea M, Reghellin D, Gobbo S, Zamboni G, Chilosi M, Bonetti F. Molecular pathology of lymphangioleiomyomatosis and other perivascular epithelioid cell tumors. Arch Pathol Lab Med. 2010; 134:33–40.

[10] McCormack FX, Inoue Y, Moss J, Singer LG, Strange C, Nakata K, Barker AF, et al. Efficacy and safety of sirolimus in lymphangioleiomyomatosis. N Engl J Med. 2011;364(17):1595-1606

[11] McCormack FX, Gupta N, Finlay GR, Young LR, Taveira-DaSilva AM, Glasgow CG, Steagall WK, Lymphangioleiomyomatosis Diagnosis and Management. Am J Respir Crit Care Med. 2016; 194(6):748-761.

[12] Cooley J, Gary Lee YC, Gupta N ,Spontaneous pneumothorax in diffuse cystic lung diseases. Curr Opin Pulm Med. 2017; 23:323–333.

[13] Gonano C, Pasquier J, Cécile Daccord, et al Air travel and incidence of pneumothorax in lymphangioleiomyomatosis... Orphanet J Rare Dis. 2018; 13:222. [

[14] Efficacy of sirolimus for the prevention of recurrent pneumothorax in patients with lymphangioleiomyomatosis: a case series. Zhou L, Ouyang R, Luo H, et al. Orphanet J Rare Dis. 2018; 13:168. [

[15] MP, Hedin CJ, et al Maximal oxygen uptake and severity of disease in lymphangioleiomyomatosis. Taveira-DaSilva AM, Stylianou. Am J Respir Crit Care Med. 2003;168:1427–1431

[16] Long-term efficacy and safety of sirolimus therapy in patients with lymphangioleiomyomatosis. Hu S, Wu X, Xu W, et. Orphanet J Rare Dis. 2019; 14:206. [

[17] Zhang L, Liang Y, Zhong X and Liu J: Literature review of clinical and pathological features of pulmonary lymphangioleiomyomatosis for 130 cases in China in the last thirty years. Chin Gen Pract. 3:329–334. 2015

[18] Francis X. McCormack , William D. Travis , Thomas V. Colby , Elizabeth P. Henske , and Joel Moss Lymphangioleiomyomatosis Calling It What It Is: A Low-Grade, Destructive, Metastasizing Neoplasm American Journal of Respiratory and Critical Care Medicine , Volume 186, Issue 12 October 05, 2012

[19] Laura J. Libby , Navneet Narula , Helen Fernandes , James Gruden , David Wolf , Daniel M. Libby Imatinib Treatment of Lymphangiomatosis American Journal of Respiratory and Critical Care Medicine 2016;193:A50